Surgery for Obesity and Related Diseases 17 (2021) 299–307

SURGERY FOR OBESITY AND RELATED DISEASES

Original article

Circulating magnesium status is associated with type 2 diabetes remission after Roux-en-Y gastric bypass surgery: a long-term cohort study

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Received 19 May 2020; accepted 29 September 2020

Abstract

Background: Low serum magnesium levels predict cardiovascular and all-cause mortality in patients with typ 2 diabetes.
Setting: Outpatient clinic of obesity and central hospital.
Objectives: To assess long-term alterations in circulating magnesium status after Roux-en-Y gastric bypass (RYGB) surgery and associations with remission of type 2 diabetes (T2D).
Methods: Retrospective analysis of 5-year outcomes of plasma magnesium (p-Mg) and glucometabolic statuses in patients who underwent primary RYGB and who completed the annual follow-up program. Data were investigated from 84 patients without diabetes and 62 with T2D before RYGB, who showed either prolonged remission (n = 30), temporary remission (n = 16), or no remission (n = 16) after surgery.
Results: Body mass indexes before RYGB were similar in patients with and without T2D, irrespective of remission. The patients not achieving remission showed longer diabetes durations; higher circulating glucose levels; more intensive antidiabetic drug treatment, including insulin; and significantly lower p-Mg concentrations (.73 [±.08] mmol/L compared with .80–.82 [±.07] mmol/L, respectively; $P < .01$) than the groups showing remission or without diabetes before surgery. After RYGB, the p-Mg increased similarly, by 10–12% in the groups with T2D before surgery, irrespective of remission; however, the nonremission group did not reach the p-Mg levels registered in the other groups after follow-up. The nonremission group reached .82 (.09) mmol/L, compared with .87 (.06) and .88 (.08) mmol/L ($P < .05$), respectively, in patients with remission or without a history of diabetes.
Conclusion: The p-Mg concentrations increased after RYGB, with similar increments irrespective of T2D remission; however, the nonremission group started from an inferior level and did not reach the p-Mg concentrations seen in the groups achieving remission or without a history of diabetes before surgery. (Surg Obes Relat Dis 2021;17:299–307.)

Key words: Gastric bypass; Magnesium; Diabetes; Diabetes remission; Obesity

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https://doi.org/10.1016/j.soard.2020.09.036

Bariatric surgery has been shown to reduce cardiovascular and cancer mortality rates and lower the incidence of type 2 diabetes (T2D) [1–3]. It was early observed that Roux-en-Y gastric bypass (RYGB) surgery could improve the glucometabolic status and induce remission of T2D [4,5]. Remission rates between 43.2% and 84% have been reported after RYGB, with heterogeneity regarding the definition of diabetes remission [6].

Several studies have tried to identify predictive factors for T2D remission after bariatric surgery. From the Swedish Obese Subjects study, it was concluded that the positive effects for both prevention and remission of T2D are independent of body mass index (BMI) before surgery [7]. Similar observations were reported by Panunzi et al. [8] from a meta-analysis comprising 4944 patients with T2D from 94 bariatric studies, with a diabetes remission rate not depending on the BMI limit of 35 kg/m^2.

The Swedish National Board of Health and Welfare recommend treatment with bariatric surgery in patients with T2D and a BMI $>$ 40 kg/m^2. This kind of treatment could also be performed in patients with T2D and with a BMI 35–40 kg/m^2; however, in both cases a structured follow-up is mandatory. Laparoscopic RYGB is still the most commonly performed surgical procedure in Sweden for patients with obesity World Health Organization classes III and IV: that is, with a BMI $>$ 35 kg/m^2.

Epidemiologic and clinical studies have indicated lower extra- and intracellular magnesium concentrations in patients with insulin-resistant conditions like T2D [9–11]. Magnesium acts as a cofactor for a large number of enzymes involved in the carbohydrate, lipid, and protein metabolism [12]. Hypomagnesemia, per se, might also contribute to impaired insulin sensitivity, thus creating a vicious circle and worsening the glucometabolic status further [13]. The inverse association between dietary magnesium intake and the risk of T2D has repeatedly been reported [14]. It has also been suggested that magnesium deficiency may contribute to the development of diabetic complications [15–17]. Lower circulating magnesium concentrations have also been associated with left ventricular hypertrophy and coronary artery calcification, and predict cardiovascular and all-cause mortality in patients with T2D, when conventional cardiovascular risk factors are taken into account [18–21].

Previous observations have indicated increased circulating magnesium levels or decreased prevalences of magnesium deficiency after RYGB [22–26], while a study comprising patients with and without T2D reported improved serum magnesium levels only in those patients in whom diabetes was resolved after surgery [24]. Previously, we reported that the lowered plasma magnesium (p-Mg) status associated with impaired glucometabolic status in patients with T2D was increased after RYGB, reaching similar concentrations as in patients without a history of diabetes after 1 year [26], but with both groups still below the recently proposed level of .85 mmol/L when regarding the risk of cardiovascular disease [27]. However, these patients were not stratified regarding the degree of diabetes remission.

The aim of the present study was to investigate long-term alterations in circulating magnesium status during a follow-up of 5 years after RYGB. A second aim was to explore associations between remission of T2D and alterations in magnesium status after this kind of bariatric surgery.

Methods

Study design

We conducted a retrospective analysis of 5-year outcomes of p-Mg and glucometabolic statuses in all consecutive patients who underwent primary RYGB and who completed the follow-up visits, including biochemical test panels at 6 and 12 months and then annually after surgery.

Patients

The data were collected from patients who were consecutively screened for bariatric surgery during 1 calendar year, January–December 2011, at the Bariatric Outpatient Clinic, affiliated with the Department of Surgery, Central Hospital, in Falun, Sweden. The surgeries were performed in 2011 or 2012 at the Department of Surgery, Mora hospital, Mora, or the Department of Surgery, Central Hospital in Falun, Sweden. In case of a delay for surgery of more than 6 months after approval, the investigational procedures were repeated and the database was updated accordingly. Patients treated with other operations than RYGB or conversions were not included in this RYGB subset of the cohort. An annual follow-up program for 5 years was performed on a routine basis, as for all our patients treated with bariatric surgery. The results from the 1-year follow-up after RYGB in this cohort have been reported previously [26]. The statistics in this report are based on data from those patients who were treated with RYGB and who fulfilled the annual follow-up program of 5 years, including anthropometric data, lifestyle and medication questionnaires, and biochemical test panels.

T2D was defined according to the World Health Organization criterium from 2006 and 2014 (fasting plasma glucose $\geq$ 7.0 mmol/L or glycosylated hemoglobin [HbA1C] $\geq$ 6.5% [48 mmol/mol]), or was based on medical history and treatment with antidiabetic pharmacotherapy. Remission of diabetes was defined as having HbA1C $<$ 6.0% (42 mmol/mol), without antidiabetic medications, during at least 1 year. We classified remission as "prolonged" when the state of remission remained until the follow-up at 5 years after RYGB and as "temporary" if the state of remission could not be maintained until this final follow-up.

Laparoscopic Roux-en-Y gastric bypass surgery

RYGB was carried out as previously described in detail [26]. All patients were given the same kind of dietary advice and were prescribed vitamin B12 for parenteral, intramuscular administration, at a dose of 1 mg every third month.

All patients were also recommended to take an oral supplement containing vitamins and minerals (2 tablets daily, each tablet containing 58 mg magnesium, Mitt Val Kvinna, Meda OTC AB, Solna, Sweden). Additional supplements (zinc, iron, calcium, vitamin D, folic acid) were prescribed pro re nata. Information regarding actual medications—prescribed drugs as well as self-care—was obtained annually.

Variables

Body mass index

BMI (kg/m^2) was calculated as weight (in kilograms) divided by height (in meters) squared. Excess BMI (EBMI) was defined as the BMI over the ideal weight, defined as a BMI of 25 kg/m^2. The percentage of excess BMI lost (%EBMIL) was calculated as the change in EBMI after surgery / (EBMI before surgery $\times$ 100).

Routine laboratory tests

Routine chemical tests, including hemoglobin, fasting blood glucose (fP-glucose), HbA1C, p-Mg, creatinine, and lipid concentrations, were all carried out at the Department of Clinical Chemistry at the Central Hospital Falun.

Statistics

Means and standard deviations were used for descriptive measurements. Continuous variables were tested for normality (Shapiro-Wilk's test, w value .95). Mean changes in variables were analyzed by the paired Student t test, or by a Wilcoxon signed rank test if the data were not normally distributed. Bivariate correlations are expressed as Pearson's correlation coefficient. Nonparametric measures of associations were used in cases of nonnormally distributed variables (Spearman's rank-order correlations). Tests were 2-tailed, and a P value $< .05$ was considered to indicate statistical significance. Either a χ^2 test or Fisher's exact test was used when comparing qualitative variables. Logistic regression for a nominal response (T2D remission/no T2D remission) was carried out regarding predictors for diabetes remission. To elucidate the interdependence of variables correlated to p-Mg before RYGB, a stepwise multiple regression analysis was performed. The statistical software JMP 5.0 for PC (SAS Corporation, Cary, NC) was used for all statistical calculations.

Ethics

The study was approved by the board of ethics at Uppsala University, 2017/108.

Results

Patients metabolic characteristics and magnesium status before RYGB

In total, 174 patients, of whom 67 had a diagnosis of T2D and 107 were without a history of diabetes, were treated with RYGB. During the follow-up period of 5 years, 4 patients died: 3 with T2D and 1 without. Before the end of the follow-up, 7 patients from the group without T2D and 2 patients with T2D left our region. An additional 4 patients without a history of T2D did not complete the follow-up visits for unknown reasons. Thus, 95 patients (60%) without T2D and 62 patients (40%) with T2D before RYGB were evaluated regarding incidences or remission of T2D during the follow-up period of 5 years (Fig. 1).

There were no new cases of T2D in the group without such a diagnosis before RYGB. Of the patients with T2D before RYGB, 30 (48%) showed prolonged remission, 16 (26%) showed temporary remission, and 16 (26%) did not achieve remission (Fig. 1). The characteristics for these groups are shown in Table 1. P-Mg assessments were added to the biochemical test panels for 84 of the 95 patients without T2D before RYGB and for all patients with a history of T2D. One patient with T2D who did not achieve remission developed renal insufficiency 3 years after RYGB, and his p-Mg data were allowed to expire for this reason.

The patients with T2D before surgery were older than the patients without diabetes; however, there were no statistically significant differences between the 3 groups of patients with T2D before surgery (Table 1). Anthropometric measurements regarding weight or BMI did not show any significant differences between patients with or without diabetes or between the 3 groups regarding diabetes remission (Table 1 and Fig. 2A).

The diabetes duration was significantly longer in the group showing no remission, but the duration ranges were similar in the 3 groups with diabetes before surgery. The mean fP-glucose concentration and HbA1C level were significantly higher before surgery in the group showing no remission, compared with the groups achieving temporary or prolonged remission (Table 1 and Fig. 2B). Insulin treatment and oral antidiabetic drugs were more common in the group without remission, while lifestyle regimens without drugs were more common in the group showing prolonged remission (Table 1). Diabetes duration maintained as a significant ($P < .02$) predicting factor for diabetes remission in a nominal logistic model.

The patients not achieving diabetes remission showed significantly lower p-Mg levels before surgery (.73 [$\pm$.08] mmol/L), compared with the patients showing temporary remission (.80 [$\pm$.07] mmol/L) or prolonged remission (.80 [$\pm$.07] mmol/L; $P < .01$). The p-Mg levels in the latter 2 groups did not significantly differ from the mean value in the group of patients without a history of diabetes (.82 [$\pm$.06] mmol/L; Table 1 and Fig. 2C). The relative number of patients showing hypomagnesemia, defined as p-Mg $< .75$ mmol/L, was highest (50%) in the T2D group without remission and lowest (7%) in patients without a history of T2D ($P < .001$; Table 1). The p-Mg level before surgery was inversely correlated to the diabetes duration (r = - .50; $P < .0001$), HbA1C (r = - .36; $P = .0001$),

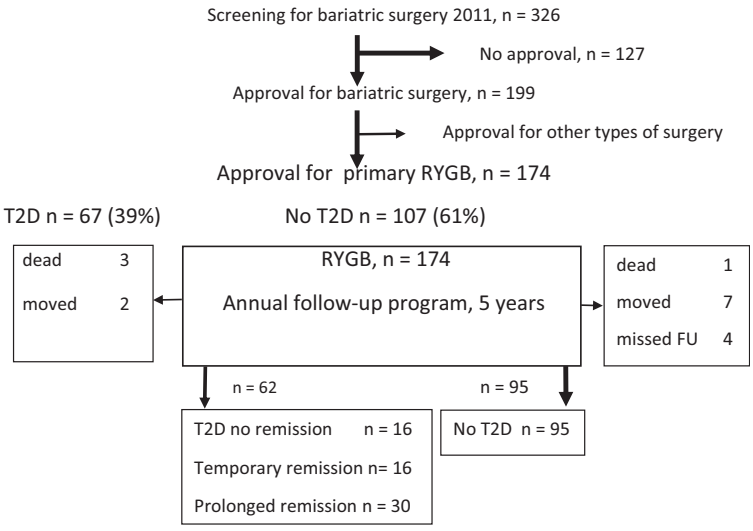

Fig. 1. Organizational chart. RYGB = Roux-en-Y gastric bypass; T2D = type 2 diabetes; FU = follow-up.

fP-glucose (r = - .34; P = .0001), and BMI (r = - .19; P = .03). The inverse correlation between p-Mg before RYGB and diabetes duration remained significant ($P < .0002$) when these variables were tested in a stepwise multiple regression model, indicating a mean reduction of p-Mg of .007 mmol/L for each year of diabetes duration. The p-Mg was unrelated to the use of antihypertensive and lipid-lowering medications.

The systolic and diastolic blood pressure levels were similar in the 4 groups, but a majority (55–79%), of the patients with diabetes were on antihypertensive medications, compared with 29% of the patients without diabetes ($P < .05$). The mean plasma triglyceride concentration was higher in the patients with T2D before surgery, although lipid-lowering drug treatment was more common among these patients (Table 1). The relative number of smokers did not differ.

Glucometabolic and magnesium alterations after RYGB

The mean BMI fell equally, by 25%–30%, during the first postoperative year in patients with or without T2D, irrespective of the degree of diabetes remission (Fig. 2A). Most of the weight reduction occurred during the first 6 months after surgery. Nadir levels were reached after 12–24 months in patients without diabetes and in patients showing remission, while patients not achieving remission showed their lowest BMI values somewhat later (Fig 2A). Similar EBMILs were observed in the 4 groups 24 months after surgery; however, the group with temporary remission showed a significantly lower EBMIL after 5 years (Table 1).

The glucometabolic alterations in the different groups of patients are shown in Fig. 2B. The alterations in HbA1C during the first postoperative year were explained by changes in fP-glucose (r = .63; $P < .0001$) but were unrelated to changes in hemoglobin levels (r = .02; P = .829). The fP-glucose increment from nadir until the follow-up at 5 years was correlated to the change in BMI during this corresponding period (r = .37; $P < .0001$).

The number of antidiabetic drugs was reduced in all groups of patients with T2D before surgery (Table 1). None of the patients in the group showing prolonged remission used, by definition, any such drugs at the follow-up at 5 years. All patients in the group showing temporary remission were without any antidiabetic medications at 24 and 36 months after surgery, while 1 of 16 patients used metformin at 48 months, and 3 of 16 were on this medication after 5 years. The relative number of patients using insulin in the group not achieving remission decreased from 50% before surgery to 19% after 5 years (Table 1).

The p-Mg concentrations increased during the entire follow-up of 5 years by 7% (±8) in the group without a history of diabetes, compared with 11% (±11) in the group with T2D before RYGB (P = .012), without any significant differences between the groups with different degrees of diabetes remission. However, the group not achieving remission did not at any time during the follow-up catch the p-Mg levels registered in the other groups, although showing a similar p-Mg increment. The group not achieving remission reached .82 (.09) mmol/L, compared with .87 (.06) and .88 (.08; $P < .05$) mmol/L, respectively, in patients showing remission or without a history of diabetes (Fig 2C). Despite increased magnesium levels, 2 patients (14%) in the T2D group without remission showed p-Mg < .75 mmol/L 5 years after surgery. The alterations in p-Mg were not explained by changes in circulating creatinine levels, nor the use of antihypertensive medications.

The group achieving prolonged remission showed a pronounced decline regarding the use of lipid-lowering drugs, reaching a similar level as the group without diabetes (14% and 10%, respectively; not significant). The fP-triglyceride

Table 1
Characteristics, metabolic variables, and drug treatment before Roux-en-Y gastric bypass and at 5 years post surgery

Variable	T2D no rem	T2D temp rem	T2D prol rem	No T2D	*P* for difference
n	16	16	30	95	
Age, yr	52 (8)^{y}	51 (8)^{y}	47 (10)^{y}	43 (12)^{x}	x versus y: $P < .01$
Female, %	56	50	73	71	
Diabetes duration, mean (range)	10.0 (0–19)^{y}	3.7 (0–18)^{x}	3,0 (0–16)^{x}	-	x versus y: $P < .01$
fP-glucose, mmol/L	10.6 (4,0)^{y}	9.0 (3,1)^{z}	9,2 (2,9)^{z}	5,9 (0,5)^{x}	x versus y, z: $P < .01$; z versus y: $P < .05$
fP-glucose at 5 yr, mmol/L	8.8 (2,7)^{y}	6.8 (1,2)^{z}	5,7 (0,5)^{x}	5,4 (0,5)^{x}	x versus y, z: $P < .01$; z versus y: $P < .05$
B-HbA1C, mmol/mol	69 (15)^{y}	58 (15)^{z}	55 (15)^{z}	38 (4)^{x}	x versus y, z: $P < .01$; z versus y: $P < .01$
B-HbA1C at 5 yr, mmol/mol	57 (7)^{y}	46 (3)^{z}	39 (3)^{u}	37 (3)^{x}	y versus z, u, x: $P < .01$; z versus u, x: $P < .01$; u versus x: $P < .05$
Insulin treatment, %	50^{y}	31^{z}	7^{x}	-	y versus z: $P < .05$; y, z versus x: $P < .001$
Insulin treatment at 5 yr, %	19	0	-	-	ns
Metformin, %	81^{y}	69^{y}	43^{x}	-	y versus x: $P < .05$
Metformin at 5 yr, %	57^{y}	19^{z}	-	-	y versus z $P < .05$
Other oral antidiabetes drugs, %	25	13	17	-	ns
Other oral antidiabetes drugs at 5 yr, %	25	19	-	-	ns
Lifestyle only, %	6^{y}	20^{z}	47^{x}	-	y versus z: $P < .01$; y versus x: $P < .001$; z versus x: $P < .01$
No antidiabetic drugs at 5 yr, %	31^{y}	81^{z}	-	-	y versus z: $P < .001$
Weight, kg	121 (24)	126 (23)	130 (22)	124 (18)	ns
BMI, kg/m^2	41,7 (4,5)	42,1 (6,3)	44,9 (6,0)	43,0 (5,0)	ns
EBMIL 24-0, %	−66 (22)	−71 (27)	−72 (20)	−72 (23)	ns
EBMIL 60-0, %	−66 (26)^{x}	−43 (22)^{y}	−61 (21)^{x}	−64 (24)^{x}	x versus y: $P < .05$
Systolic blood pressure, mm Hg	139 (17)	135 (24)	138 (21)	134 (16)	ns
Diastolic blood pressure, mm Hg	81 (6)	79 (11)	84 (12)	81 (10)	ns
Antihypertensive drugs, %	81^{y}	81^{y}	57^{z}	31^{x}	y versus z: $P < .05$; y versus x: $P < .001$; z versus x: $P < .05$
Antihypertensive drugs at 5 yr, %	56^{u}	75^{y}	43^{z}	21^{x}	u, y, z versus x: $P < .01$; y versus z: $P < .05$; u versus y, z: ns
fP-triglycerides, mmol/L	2,4 (2,1)^{y}	2,1 (1,3)	2,5 (1,3)^{y}	1,7 (0,8)^{x}	x versus y: $P < .01$
fP-triglycerides at 5 yy, mmol/L	1,5 (0,7)	1,6 (0,8)^{y}	1,4 (0,7)	1,2 (0,6)^{x}	x versus y: $P < .05$
Lipid-lowering drugs, %	69^{y}	44^{z}	33^{z}	10^{x}	y, z versus x: $P < .001$; y versus z: $P < .05$
Lipid-lowering drugs at 5 yr, %	53^{y}	38^{y}	14^{x}	10^{x}	y versus x: $P < .001$
P-Mg, mmol/L	0,73 (0,08)^{y}	0,80 (0,07)^{x}	0,80 (0,07)^{x}	0,82 (0,06)^{x}	x versus y: $P < .01$; no T2D: n = 84
P-Mg < .75 mmol/L, %	50^{y}	20^{z}	19^{z}	7^{x}	y versus z, x: $P < .001$; z versus x: $P < .05$
P-Mg < .75 mmol/L at 5 yr, %	14^{y}	7^{y}	0^{x}	1^{x}	y versus x: $P < .05$
P-creatinine, mmol/L	65 (11)	70 (18)	63 (10)	67 (11)	ns

T2D = type 2 diabetes; rem = remission; temp = temporary; prol = prolonged; f = fasting; P = plasma; B- = blood; HbA1C = glycosylated hemoglobin; ns = not statistically significant; BMI = body mass index; EBMIL = excess BMI loss; 24-0 = the change from before RYGB to 24 mo after surgery; 60-0 = the change from before RYGB to 60 mo after surgery; Mg = magnesium.

levels increased from a nadir level of 1.1 mmol/L at 6 months after surgery to 1.6 mmol/L at the end of the follow-up in the group with temporary remission, with a similar pattern for the changes in glucometabolic variables. The corresponding fP-triglyceride changes in the other groups were minor. The increase in lipid levels from nadir until the 5-year follow-up was, in congruence with fP-glucose alterations, correlated to the change in BMI during this corresponding period (r = .38; $P < .0001$).

Discussion

The main finding in this 5-year retrospective study was that p-Mg concentrations continued to increase after the first year after RYGB, with similar increments irrespective of T2D remission. However, the patients not achieving remission did not reach the p-Mg levels observed in patients showing remission or in those without a history of T2D. The patients without remission showed an inferior p-Mg level even before surgery, determined by a longer diabetes duration and a more deteriorated glucometabolic status.

The findings after the first postoperative year are partly in accordance with recent observations by Mikalsen et al. [28], who reported a more pronounced serum magnesium increase 12 months after RYGB in patients with T2D, reaching the same magnesium levels as in patients without diabetes. The present long-term follow-up regarding alterations in circulating magnesium concentrations after RYGB also showed a further increase after the first postoperative year, reaching somewhat of a plateau after 36 months. Similar p-Mg levels were found in patients achieving temporary or prolonged remission is in the group without a history of diabetes, and after 36 months these groups showed mean p-Mg concentrations $\geq$ 0.85 mmol/L, an evidenced-based reference

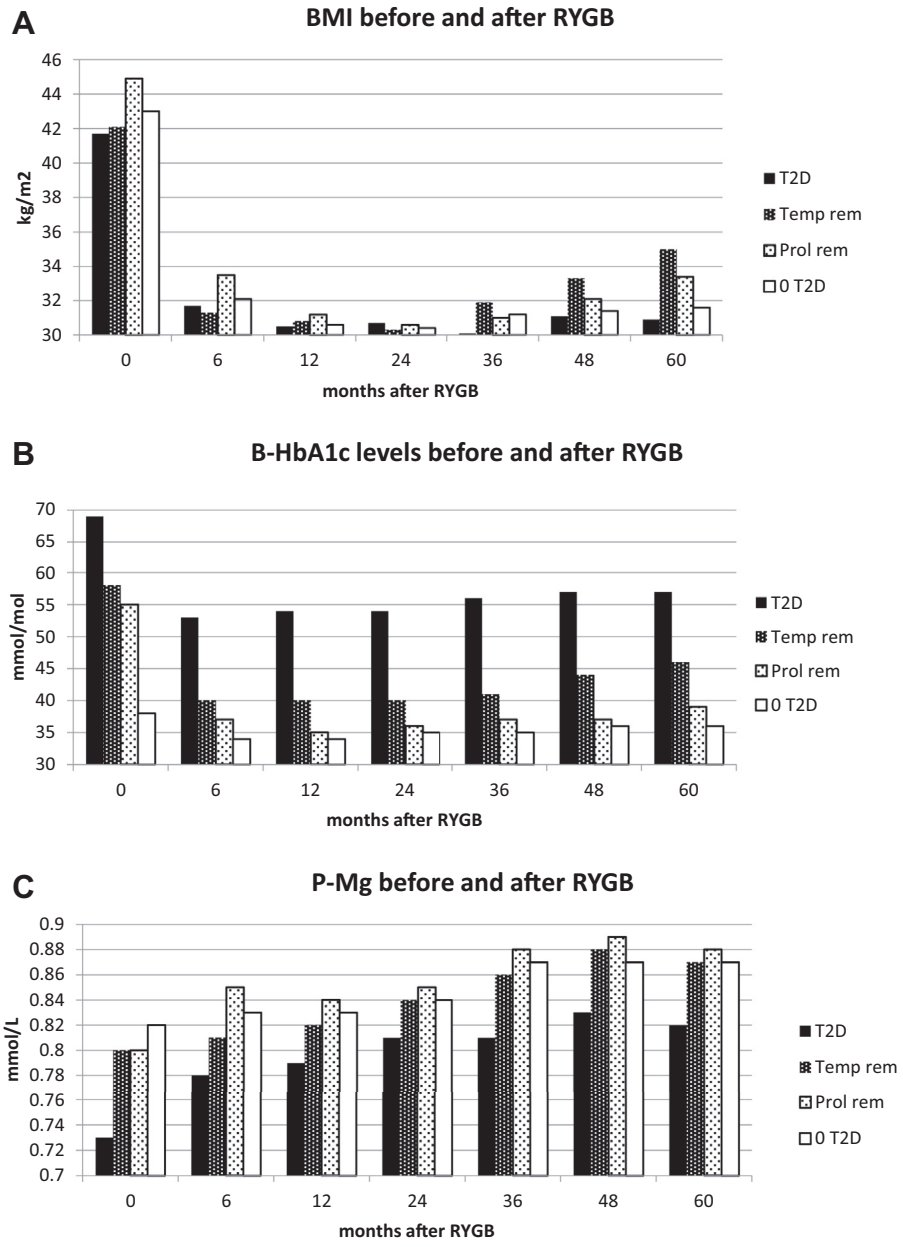

Fig. 2. Variables before and after RYGB in patients with T2D before RYGB and not achieving remission after surgery (T2D), showing temporary remission (Temp rem), prolonged remission (Prol rem), or without a history of diabates (0 T2D). (A) There were no intergroup differences in BMI at any of the different timepoints. (B) B-Hba1C levels, with 30 mmol/mol corresponding to 4.9% (DCCT), 35/5.4; 40/5.8; 45/6.3; 50/6.7; 55/7.2; 60/7.6; 65/8.1; 70/8.6, respectively. At every time point, B-HbA1C was significantly ($P < .01$) higher in T2D compared with the other groups. The T2D groups achieving remission, whether temporary or prolonged, showed similar B-HbA1C levels (ns) before surgery (0). Those with prolonged remission showed significantly lower B-HbA1C levels at all time points after surgery (6–60), compared with those in the temporary remission group ($P < .05$–$.10$), but higher levels than the 0 T2D group before surgery (0) and 6 and 60 months postsurgery ($P < .05$–$.01$) and similar levels to the 0 T2D group at 12, 24, 36, and 48 months. (C) No intergroup differences in P-Mg were noted at any time point between the Temp rem, Prol rem, or 0 T2D groups. The T2D group showed lower p-Mg at every time point; however, the differences were statistically not different from the concentrations found at 6, 12, and 24 months in the Temp rem group and at 24 months in the 0 T2D group. RYGB = Roux-en-Y gastric bypass; T2D = type 2 diabetes; BMI = body mass index; B-HbA1C = glycosylated hemoglobin; p-Mg, plasma magnesium concentraion; DCCT = Diabetes Control and Complications Trial; ns, not significant.

interval proposed to reduce the risk of cardiovascular diseases [27]. The patients not achieving remission showed similar p-Mg increments but started from an inferior level before surgery and reached a maximum level of .82 (±.09) mmol/L, thus were below the proposed level.

There are few previous reports regarding long-term alterations in circulating magnesium status after bariatric surgery. The present observations are in accordance with those reported by Moizé et al. [25], who found a decreased prevalence of hypomagnesemia during a 5-year follow-up

after RYGB, from 29.4% before surgery to 14.1% at 12 months and 5.8% after 60 months, despite a lowered daily dietary magnesium intake after surgery, or an approximately unchanged total intake when the daily magnesium supplementation of 80 mg was taken into account.

The inverse association between glucometabolic status and p-Mg concentrations has been reported previously, with lowered circulating magnesium concentrations repeatedly observed in patients with T2D [9–11,24]. This relationship might be explained by the increased renal magnesium excretion observed at hyperglycemia, also without glucosuria, and hyperinsulinemia [29–31]. Intensified treatment with insulin or oral hypoglycemic drugs, such as metformin, may not reverse this hypomagnesemia [31,32]. The reversed hypomagnesemia observed in patients treated with RYGB is probably caused by an improved glucometabolic condition, characterized by lowered circulating glucose and insulin concentrations [22].

Since magnesium acts as a cofactor for a large number of enzymes involved in the carbohydrate metabolism, it might be hypothesized that the increased circulating magnesium status, per se, might help to improve the glucometabolic status further, thus creating a reversed vicious circle. From nonbariatric studies on patients with T2D, Paolisso et al. [33] reported an increased glucose disappearance rate after magnesium supplementation, which increased p-Mg to .83 mmol/L, compared with .78 mmol/L with placebo. However, de Valk et al. [34] reported no improvement in glycemic control from a placebo-controlled study on insulin-requiring patients with T2D, although p-Mg increased from .78 to .82 mmol/L by magnesium supplementation. The varied glucometabolic effects reported from several trials with magnesium supplementation are probably explained by differences in magnesium salt formulations, dosages, and baseline magnesium statuses [35]. From a meta-analysis of double-blind randomized controlled trials on the effects of magnesium supplementation on glucose metabolism, it was concluded that glucose parameters improved in patients with diabetes, while improved insulin sensitivity was observed in patients at a high risk of diabetes [35].

According to recommendations for supplementation of micronutrients after bariatric surgery, all patients in the present study were treated with a multivitamin supplementation program also including magnesium, at 116 mg daily, which might have contributed to the magnesium and glucometabolic alterations. The patients not achieving diabetes remission showed a similar p-Mg increment as the other groups, although from a lower baseline level, which might indicate that the magnesium supplementation should not be excluded as a contributor regarding the long-term alterations in p-Mg. The incapacity in the group not achieving diabetes remission to reach the same p-Mg as found in the groups showing remission may indicate a more severe state of diabetes, with hypomagnesemic mechanisms which could not be fully counteracted by the RYGB regimen, including the supplementation program.

The group showing no remission had a longer mean diabetes duration; a higher cardiovascular risk profile, as reflected by more frequent use of antihypertensive and lipid-lowering drugs; higher HbA1C levels; and lower P-Mg concentrations. Thus, T2D remission after RYGB might be predicted by diabetes duration, degree of glucometabolic status, and the cardiovascular risk profile rather than BMI, which is in accordance with the report by Debédat et al. [36]. However, a long diabetes duration may not exclude the possibility of diabetes remission after RYGB, since the diabetes duration ranges were similar in the groups with different degrees of remission.

Antihypertensive and lipid-lowering drugs might influence the possibilities for diabetes remission. Hydrochlorothiazide and beta blockers have well-known effects on decreasing insulin sensitivity and glucose tolerance; however, these drugs were not frequently used and there were no differences in use between the groups [37]. The most frequently prescribed antihypertensive drug was enalapril, a subgroup of angiotensin-converting enzyme inhibitors without negative effects on insulin sensitivity [38]. All lipid-lowering drugs were from the statin group, which might be of interest in this case since this kind of medication has been shown to decrease insulin sensitivity in patients with T2D [39].

Previous studies regarding the T2D remission rate after bariatric surgery have shown a range from 24% to 84% with different types of surgery, follow-up durations, characteristics of the patients, and heterogeneity in defining diabetes remission [6]. Some factors have emerged as common predictors for diabetes remission: better glycometabolic status before surgery, no or few antidiabetic drugs, younger age, shorter diabetes duration, and higher preoperative BMI [6]. Different prediction models of diabetes remission after bariatric surgery have been proposed, such as DiaRem (diabetes remission score), AdDiaRem (advanced DiaRem), ABCD (score based on age at operation, baseline BMI, C-peptide level, and diabetes duration), and IMS (individualized metabolic surgery scoring system), but these models do not take cardiovascular co-morbidities into account [6]. Since the circulating magnesium status is easily measured and information about the use of antihypertensive and lipid-lowering drugs is available in the clinic, we suggest that these factors might be considered in predictive models.

The risk for diabetes relapse was related to the degree of weight regain after reaching the nadir level, which is accordance with previously reported observations [40].

Limitations

Although a correlation was found between the alterations in glucometabolic status and p-Mg, the explaining

mechanisms still need to be explored, since dietary magnesium intake, renal magnesium excretion, and intracellular magnesium concentrations were not measured in this study, nor did we investigate mechanisms such as alterations in magnesium absorption due to the anatomic changes after RYGB surgery. These topics could be suggested for upcoming studies. Moizé et al. [25] reported a lowering prevalence of hypomagnesemia 5 years after RYGB, although with unchanged or decreased total magnesium intakes, which indicates that other factors than dietary magnesium intake may explain the increased circulating magnesium concentrations observed after bariatric surgery.

Conclusion

The p-Mg concentrations, known to increase during the initial postoperative year after RYGB in patients with T2D, continued to increase during the 5-year follow-up, with similar increments irrespective of diabetes remission. However, the patients not achieving remission showed an inferior p-Mg level before RYGB, which was related to diabetes duration and glucometabolic status, and did not reach the p-Mg levels found in the patients showing remission or in patients without a history of diabetes. These observations might be of interest with reference to previous reports indicating low circulating magnesium as a predictor for cardiovascular and total mortality in patients with T2D, and with reduced risks observed in patients achieving diabetes remission after RYGB. The findings in this study showing diabetes duration as a main cause of a deteriorated glucometabolic situation, lowered circulating magnesium status, and higher cardiovascular risk profile might indicate that bariatric/diabetes surgery should be considered earlier, improving the opportunities for diabetes remission. The preoperative circulating magnesium status might serve as a predictor for T2D remission after RYGB. Weight regain should be considered and treated to prevent T2D relapse.

Acknowledgments

The authors thank secretary Desire Nelson for excellent ambition in keeping their database continuously updated.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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